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ORIGINAL ARTICLE

Elevation of Serum Free Triiodothyronine, Total Triiodothyronine, Thyroxine-Binding Globulin, and Total Thyroxine Levels in Combat-Related Posttraumatic Stress Disorder

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Background: This study was designed to assess both central and peripheral aspects of thyroid function in combat-related posttraumatic stress disorder (PTSD), with the particular purpose of finding a mechanistic explanation for an imbalance between serum levels of free thyroxine (T_4) and total T_4 previously observed in pilot work.

Methods: A total of 96 male combat veterans with PTSD diagnosed by *DSM-III-R* (72 from the West Haven, Conn, Veterans Affairs Medical Center and 24 from the Menlo Park, Calif, Veterans Affairs Medical Center) were compared with 24 male control subjects. One or more serum samples were analyzed by radioimmunoassays for levels of total T_4, free T_4, total triiodothyronine (T_3), free T_3, T_4-binding globulin, and thyrotropin.

Results: The pilot observation of moderately elevated total T_4 levels with no elevation in free T_4 levels in patients with PTSD was confirmed, suggesting the hypotheses that (1) there may be an increased peripheral conversion of free T_4 by deiodination to T_3 or (2) there may be an increased binding of T_4 secondary to elevated T_4-binding globulin levels. Our findings support both hypotheses. The PTSD groups all showed a marked and sustained elevation in levels of both total T_3 and free T_3, as well as elevated T_3/T_4 ratios, supporting the increased T_3 conversion hypothesis. The PTSD groups also showed a marked and sustained increase in T_4-binding globulin levels, supporting the increased binding hypothesis. Thyrotropin levels did not differ between PTSD and control groups.

Conclusions: These findings demonstrate an unusual pattern of thyroid alterations, featuring substantial elevations in total T_3, free T_3, and T_4-binding globulin levels, in combat-related PTSD that differs from established endocrinopathies, such as classic hyperthyroidism, T_3 thyrotoxicosis, or chronic T_4-binding globulin elevation.

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EVIDENCE OF an important relationship between traumatic stress and thyroid function has a long history.[1] The original clinical report of hyperthyroidism by Parry[2] in 1825 described the onset of symptoms in a woman 4 months after a terrifying experience in which she was accidentally thrown down the stairs in a wheelchair. This classic observation has since been extensively confirmed, as reviewed in 1927 by Bram,[3] who reported that a clear history of traumatic stress was found in 85% of more than 3000 cases of thyrotoxicosis. The precipitating conditions largely involved severe life-threatening crises, now commonly referred to as "traumatic stress," such as fires, shipwrecks, earthquakes, combat experiences, and narrow escapes from accidents, as well as various types of object loss. Extreme fear concerning biologic survival appeared to be the most striking common feature associated with these stressful experiences. Recent research continues to confirm the observation that more patients with hyperthyroidism give a history of major traumatic stress than do members of a control population.[4] Important relationships between the thyroid system and stress have also been

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SUBJECTS AND METHODS

Because the conditions of patient recruitment and ward milieu may differ widely from one study to another, and because hormonal systems are so sensitive to even relatively subtle psychosocial influences, our experience has indicated that it is important to describe these factors in some detail in characterizing PTSD patient samples.

RECRUITMENT OF PATIENTS WITH PTSD

Four samples of male combat veterans with PTSD were studied by the National Center for PTSD, including three successive samples, each composed of 24 patients, admitted to the West Haven Veterans Affairs Medical Center inpatient treatment program, along with one sample of 24 patients admitted to the Menlo Park (Calif) Veterans Affairs Medical Center inpatient treatment program. As a comparison group, 24 normal control subjects were studied. Informed consent was obtained from all patients and control subjects.

The diagnosis of PTSD was established by means of *DSM-III-R* criteria on the basis of the Structured Clinical Interview for *DSM-III-R*.[17] Other clinical assessments included the Mississippi Scale for Combat-Related PTSD,[18] the Clinician-Administered PTSD Scale,[19] and the Combat Exposure Scale.[20] Overall mean scores relating to the severity of PTSD were 132 for the Mississippi Scale, 30 for the Combat Exposure Scale, 41 for the Clinician-Administered PTSD Scale frequency sum, and 34 for the Clinician-Administered PTSD Scale intensity sum. There were no significant differences in these scores between the three West Haven groups, but the Menlo Park values were generally slightly lower (Mississippi Scale, 94%; Combat Exposure Scale, 84%; Clinician-Administered PTSD Scale frequency sum, 73%; and the Clinician-Administered PTSD Scale intensity sum, 87%) than those for the West Haven groups, perhaps because of minor differences in the approach to patient selection. With regard to the comorbid rate of other psychiatric illnesses in the overall patient sample, diagnostic criteria were met by 79% for previous alcohol abuse, 40% for major depressive disorder, 25% for polysubstance abuse, and 19% for anxiety disorder.

Exclusion criteria included psychotic disorders, major medical illnesses, hormonal medication, organic brain syndrome, and current drug or alcohol abuse less than 3 months before the study. Urine toxicologic screening for substance abuse was done on admission and at intervals during the hospitalization period. About 50% of the patients had been taking some psychiatric medication previously, mostly antidepressants or benzodiazepines, and the 72 patients in the West Haven sample were required to begin withdrawal 3 weeks before entering the protocol and to remain without medication during the study. The Menlo Park group was permitted to continue medication at the time of the study, but they showed no significant differences in thyroid hormone levels from the West Haven sample.

All the patients with PTSD were recruited for participation in research-oriented inpatient treatment programs of about 3 months' duration in the Veterans Affairs National Center for PTSD. None of the patients was admitted in an acute crisis stage, and all were screened for scheduled admission with a requirement that there was some current level of stability in their life.

SELECTION FACTORS AND WARD MILIEU

Selection factors included favoring patients who were judged not likely to create serious ward management problems and who were judged likely to be able to tolerate and complete the lengthy and demanding treatment program. The West Haven treatment program was designed to deal intensively with both the primary trauma in combat and the secondary trauma connected with the return home. All patients knew ahead of time that they would be required to be free of medication, in some cases for the first time in many years. They knew that they would be involved in community activities and in close and continuing interaction with other patients within groups, as a member of a 12-patient cohort. They anticipated that they would be expected to disclose traumatic experiences and feelings related to Vietnam, in many cases things they had seldom confided to anyone in the past. They also knew that they would be expected to express their feelings concerning traumatic experiences through writing, drawing, drama, and art. The dropout rate, however, was relatively low, about 13%, and mostly involved patients who lapsed into drug

demonstrated in many preclinical studies in both normal humans and animals that have shown alterations in thyroid hormone secretion in response to a variety of psychologically stressful situations.[1] More generally, a substantial number of clinical psychoendocrine studies have examined the role of the hypothalamic-pituitary-thyroid (HPT) axis in relation to a wide variety of psychiatric illnesses, including both affective and schizophrenic disorders.[5-7] There is strong support, therefore, for considering the thyroid hormones as fully qualified "stress hormones" to be included in psychoendocrine studies, even though they have so far received much less attention than has cortisol or the catecholamines in this regard.

With this background in mind, we included free thyroxine (FT_4) and total thyroxine (TT_4) assays, as part of a profile of stress-responsive hormonal measures, in a pilot psychoendocrine study of posttraumatic stress disorder (PTSD) in combat veteran inpatients at the West Haven (Conn) Veterans Affairs Medical Center.[8] Although many years have elapsed since the actual military combat experience of Vietnam veterans with PTSD,

use early in the program. Throughout hospitalization, there was an intensive schedule of 32 hours per week of individual and group therapy, as well as substantial demands on patient time for participation in a variety of biologic or psychological research projects, so that the setting did not facilitate the use of avoidant coping strategies. The program at Menlo Park was generally similar to that at West Haven, but the milieu was perhaps less intensive in certain respects.

CONTROL SUBJECTS AND DEMOGRAPHIC FACTORS

Most of the control subjects were recruited by advertisement as participants in a concurrent challenge test research project at the West Haven Center, and baseline blood samples were obtained on an outpatient basis in the same location and by the same staff personnel as were the patient samples. Most control subjects were veterans; 13 had a negative history and 11 a positive history of combat exposure. None met *DSM-III-R* criteria for PTSD. Mississippi Scale scores ranged up to only 81, which, although possibly indicating partial PTSD in a few subjects, was well below the lower limit of the range of patient values, which was 105. All control subjects were screened to exclude both psychiatric and medical illnesses. The control group was demographically similar to the patient groups in all respects, except for a younger mean age of 38 years. However, there were no significant correlations between age and any of the hormonal measures used in this study, and statistical adjustments to correct for the age difference disclosed that this variable did not affect the significance of any of the reported hormonal differences between the patient and control groups.

The total sample of 96 patients was predominantly white (78%), with an average age of 42.5 years, weight of 84 kg, and height of 178 cm. All four samples were closely similar demographically except in race. The Menlo Park sample was 46% white, 42% Hispanic, and 8% black, but no significant differences were observed in any of the hormones measured in this study between the white and Hispanic subgroups. The total West Haven sample (n=72) was 88% white and 11% black, with all but one black patient included in the first subgroup of 24 patients.

HORMONAL MEASUREMENTS

Blood samples (10 mL) for thyroid hormone assays were collected at 8 to 9 AM in all subjects, and, after setting of the clot and centrifugation, the serum was divided into three 1.5-mL aliquots in small glass vials and frozen at −70°C until assayed. Because six different hormonal assays were to be performed on each sample, the three aliquots minimized freezing and rethawing cycles as a potential source of hormonal instability and analytic error, especially since two different hormonal assays were usually done concurrently when each aliquot was thawed for the first time. In the three West Haven groups, blood samples were obtained during the admission period from all 72 patients, during the discharge period about 12 weeks later from 63 patients, and during the midcourse period from 47 patients, while the single sample obtained from the Menlo Park group represented variable points for different individuals during the course of hospitalization, since the collections were done during a single calendar week by a visiting research team from the West Haven unit. As detailed earlier, the West Haven patients were free of medication during the period when the initial sample was obtained.

Serum TT_4, FT_4, and TT_3 concentrations were measured by RIA procedures, with the use of kits (Incstar Corp, Stillwater, Minn). The interassay coefficient of variation in our laboratory was 3.7% for TT_4, 4.2% for FT_4, and 6.0% for TT_3.

Serum FT_3 concentrations were measured by an RIA kit procedure (Diagnostic Products Corp, Los Angeles, Calif). The interassay coefficient of variation in our laboratory for FT_3 was 2.7%.

Serum thyrotropin concentrations were measured by means of a sensitive third-generation RIA kit (Incstar Corp), and the interassay coefficient of variation was 4.0% in our laboratory. The serum TBG procedure also used an RIA kit (Incstar Corp) with an interassay coefficient of variation of 3.0% in our laboratory.

Statistical comparisons were made between the control group and multiple PTSD groups by means of a one-way analysis of variance with Duncan's Multiple Range Test. Matched sample *t* tests were used for within-subject comparisons of first vs last samples, and unpaired *t* tests were used for other group comparisons. Correlational analyses were made with Pearson product-moment correlations.

it seemed reasonable to examine the possibility that PTSD, as a disorder that involves the chronic, relentless memory and reexperiencing of severely traumatic combat events, might on a long-term basis be associated with a clinically significant degree of thyroid hyperactivity even though flagrant classic thyrotoxicosis was not evident. There is an increasing body of evidence that relatively modest changes in thyroid hormone levels may have important clinical significance in relation to psychiatric disorders, even though the hormonal values remain within the "normal range," as specified for the diagnosis of glandular disease in the field of clinical endocrinology.[6] It was also of interest that the presenting clinical picture of hyperthyroidism includes such psychiatric symptoms as anxiety, irritability, explosive anger, jumpiness or exaggerated startle, restlessness, insomnia, difficulty in concentration, and other cognitive and affective disturbances commonly seen in patients with PTSD.[7] The pilot study confirmed the expectation that the patients with PTSD would have relatively high TT_4 mean levels in comparison with other diagnostic subgroups of psychiatric patients, but also yielded the unexpected and intriguing

finding that FT_4 levels were not comparably elevated.[8] It was this observation of an altered FT_4/TT_4 ratio that raised the questions leading to the present study and indicated that a more detailed assessment of thyroid function and a comparison with normal control subjects was needed to determine the pathophysiologic basis for the apparent discordance between TT_4 and FT_4 levels in PTSD.

To help visualize the rather complex physiologic issues involved in evaluating thyroid function, **Figure 1** presents a diagrammatic simplification of the secretory pathways of the HPT axis. The articulation of the thyroid system with the central nervous system through hypothalamic thyrotropin-releasing hormone (TRH), which stimulates secretion of anterior pituitary thyrotropin, which in turn stimulates the thyroid gland to release thyroxine (T_4), is well known. Less widely known, however, are the pathways from this point on that involve the fate and disposition of the large amounts of FT_4 secreted by the thyroid gland. Nearly all of the T_4 secreted is soon bound to T_4-binding globulin (TBG) in the circulating blood, whereas only a tiny percentage (0.03%) remains in free or unbound form.[10] The TT_4 value, therefore, can be viewed as essentially a measure of the level of T_4 in the bound form.

One possible explanation, then, for the discordance between the relatively high TT_4 and the relatively low FT_4 levels in PTSD might be an increase in TBG level leading to a larger overall concentration of circulating T_4 in the bound form.

A second possible explanation is provided by the fact that a substantial portion of the T_4 secreted daily, perhaps as much as one third to one half, is converted peripherally by enzymatic monodeiodination in extrathyroidal tissues to triiodothyronine (T_3), which is metabolically two to four times more powerful than T_4 and is apparently the primary agent exerting the influence of the thyroid system at the cellular level throughout the body. It is important to realize that by far the greatest source of the production of T_3, probably about 80%, is from this peripheral conversion process, so that only about 20% of T_3 is produced by central TRH-thyrotropin stimulation of the thyroid gland.[11] In fact, estimates of the percentage of T_3 produced by conversion from T_4 range as high as 90%, and Chopra[12] stated that "the generation of T_3 from T_4 peripherally accounts for most, if not nearly all, of T_3 production in normal humans." It is possible, then, that an increase in the rate of peripheral conversion of FT_4 to T_3 might explain the finding of the relatively low FT_4 levels in PTSD, if the latter hormone was being "used up" excessively to produce increased amounts of T_3. It is also of special interest that one of the factors that appears to be capable of increasing T_3 conversion is elevation of peripheral catecholamine levels,[13,14] a condition known to be present on a long-term basis in PTSD.[8]

The line of reasoning inspired by these pilot findings suggests the need to develop a methodologic approach that will deal more fully with the unusual complexity of the functional organization of the HPT system than has been possible until very recently. During the past 20 years, a substantial effort has been devoted to the study of the role of the HPT axis in the pathogenesis and treatment of affective disorders, particularly depression, with a focus largely on the central aspects of HPT organization involving TRH function. Yet some key findings in this field, such as the abnormal thyrotropin response to TRH in some depressed patients, still remain mechanistically unexplained.[7,15] Until recently, highly refined methods for thyroid hormone measurement have been limited to TT_4, with only relatively indirect methods, such as the FT_4 index or T_3 uptake measure, otherwise available for the estimate of T_4 binding, and with no sufficiently specific and sensitive methods available for the evaluation of other crucial components of the HPT system, especially for T_3. As suggested by Lipton,[16] the relatively slow rate at which we are so far "unraveling the mysteries of the HPT axis" may be in part, at least, because of the rate-limiting factor of the lack of suitable micromethods, so that the radioimmunoassay (RIA) procedures that have recently become commercially available for the measurement of FT_4, free T_3 (FT_3), total T_3 (TT_3), TBG, and thyrotropin offer considerable hope for new insights in future psychoendocrine research with this complex system. These revolutionary methodologic advances, in fact, provided a major incentive for us to pursue the present follow-up study of our earlier pilot findings in PTSD with an enlarged battery of hormonal assays, for the purposes of replication and obtaining insight into the pathophysiologic mechanisms underlying the imbalance between FT_4 vs TT_4 levels in this disorder.

RESULTS

REPLICATION OF PILOT STUDY SERUM T_4 FINDINGS

TT_4 Levels

As shown in the bar graph portion of **Figure 2**, comparison of the mean initial TT_4 level of all 96 patients (110 ± 2.4 nmol/L) with that of the 24 control subjects (87 ± 3.6 nmol/L) showed a significant elevation in the overall PTSD sample ($t=4.46$, $P<.00001$). With regard to replication of this finding in the four successive 24-patient PTSD groups, Figure 2 also presents a scatterplot of all the raw individual and group TT_4 data (1-MP represents the Menlo Park group; and 2-WH, 3-WH, and 4-WH, the three West Haven groups), showing the consistency with which these large, inde-

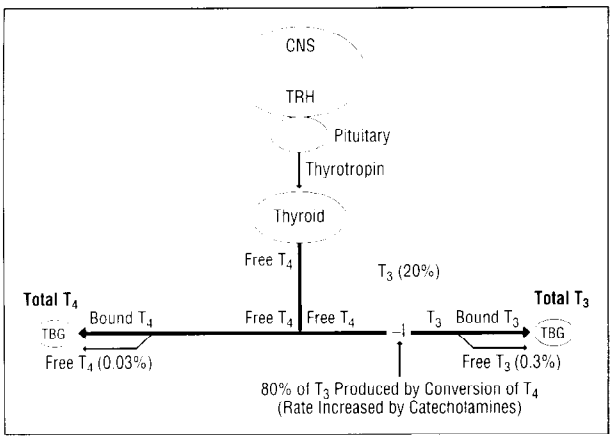

Figure 1. *Organization of the hypothalamic-pituitary-thyroid system. CNS indicates central nervous system; TRH, thyrotropin-releasing hormone; T_4, thyroxine; T_3, triiodothyronine; and TBG, thyroxine-binding globulin.*

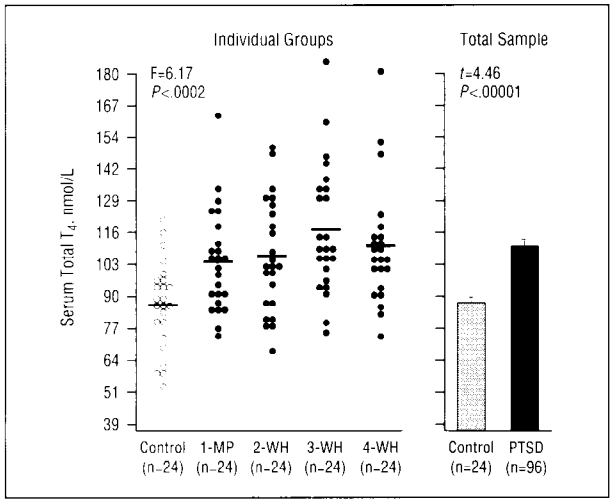

Figure 2. *Total thyroxine (T_4) elevations in four samples of patients with posttraumatic stress disorder (PTSD). 1-MP indicates first Menlo Park (Calif) Veterans Affairs Medical Center group; and 2-WH, 3-WH, and 4-WH, second, third, and fourth West Haven (Conn) Veterans Affairs Medical Center groups. Horizontal lines indicate group mean values.*

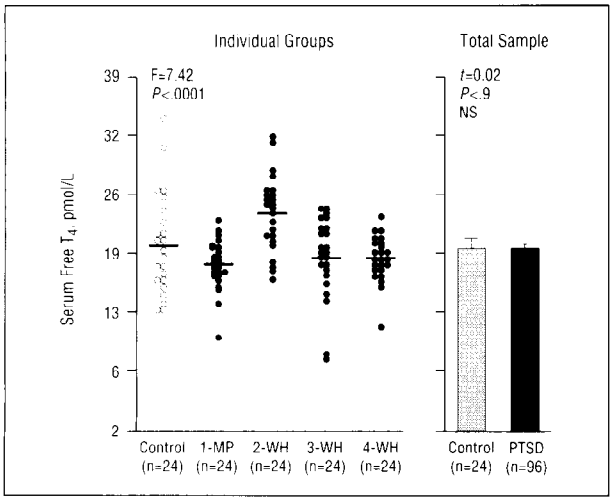

Figure 3. *Free thyroxine (T_4) levels in four samples of patients with posttraumatic stress disorder (PTSD). See Figure 2 for explanation of groups. NS indicates not significant.*

pendent PTSD patient samples had significantly higher mean levels than the control group ($F[4,119]=6.17$, $P<.0002$; controls<1-MP=2-WH=3-WH=4-WH).

The mean TT_4 levels of the PTSD groups were in the upper middle part of the clinical endocrinologic "normal range," and only 5% of the patients exceeded the upper limit of 152 nmol/L, into the zone that may indicate the presence of glandular disease. The upper limit of the control group range, however, was exceeded by 27% of the patients, and the control mean value was exceeded by 83% of the patients.

While the Menlo Park sample involved study at only a single point in time, an additional TT_4 measurement was obtained during the discharge period in a subsample (n=63) of the West Haven patients for comparison with the admission sample. The mean values for the admission period (112±2.8 nmol/L) and discharge period (110±3.1 nmol/L) showed no significant difference over time, and the discharge sample remained significantly elevated above the control mean of 87±3.6 nmol/L ($t=3.66$, $P<.0004$). Against this background of persistent moderate elevation of TT_4 levels, however, episodic fluctuations were at certain times superimposed in individual patients and in individual groups, so that future studies should search for the clinical and psychological correlates of altered TT_4 levels in PTSD within both an acute and a chronic perspective.

The present findings are similar to those in the original pilot study[8] of nine patients with PTSD, whose mean TT_4 level of 119+6.9 nmol/L does not differ significantly from the 110±2.4 nmol/L level of the present PTSD sample, while values of both of these PTSD groups are significantly higher than the control level of 87±3.6 nmol/L ($F[2,128]=11.73$, $P<.0001$). The slightly higher values in the earlier study might be accounted for by the greater symptom severity in the patients in the pilot study, who were admitted through the emergency department to a general admissions and evaluation ward for treatment during a period of acute decompensation and crisis and who generally had more functional impairment than the present patients volunteering for an elective, cohort-oriented treatment program.

FT_4 Levels

The bar graph portion of **Figure 3** presents a comparison of the mean initial FT_4 level in all 96 patients (20±0.4 pmol/L) with that of the 24 control subjects (20±1.0 pmol/L), showing no significant difference ($t=0.02$, $P<.9$); both groups had virtually identical values. With regard to replication of this finding in the four successive 24-patient PTSD groups, Figure 3 also presents all the raw individual and group FT_4 data, indicating that three of the four patient groups showed a trend to be lower than the control group, but that the first West Haven sample of 24

patients (2-WH) had a significantly elevated mean FT_4 level of 24±0.8 pmol/L ($F[4,119]=7.42$, $P<.0001$; 2-WH>control=1-MP=3-WH=4-WH). This atypically high initial level in the first West Haven group appears to represent a temporary episodic or phase elevation, since a second sample from the same group 6 weeks later showed a mean value of 19±0.9 pmol/L, similar to the initial values of the other three PTSD groups. There were no changes in study design or known situational factors related to the initial period of sample collection in the first West Haven group that might explain the finding, and the reason for this atypically high initial level remains to be determined. We did observe that most of the individual patients with the highest initial FT_4 levels in this group also tended concurrently to have the highest levels of the other thyroid measures, so that relationships between T_3 and T_4 levels, as will be discussed later, were relatively similar in all four patient groups. The generally lower levels for FT_4 in comparison with TT_4 in PTSD are further evidenced by the fact, as shown in Figure 3, that the upper limit of the control subject FT_4 range was exceeded by 0% of the patients (vs 27% for TT_4) and only 41% of the patients were above the control mean FT_4 value (vs 83% for TT_4).

With regard to change in FT_4 levels over time in the West Haven patients with PTSD (n=63) studied with both admission and discharge samples, the mean values at admission (21±0.5 pmol/L) and at discharge (20±0.5 pmol/L) indicated a significant decline in levels ($t=2.59$, $P<.01$) between the two points, but the discharge level was still not significantly different from the control mean value of 20±1.0 pmol/L ($t=0.89$, $P<.4$). While there was evidence of episodic fluctuations in FT_4 levels on occasion, these appeared generally to be not as marked or common as those observed in TT_4 levels.

These FT_4 findings appear to replicate those of the pilot study,[8] in which the mean FT_4 level for nine patients with PTSD of 19±0.8 pmol/L did not differ significantly from the 20±0.4 pmol/L of the present PTSD group or the 20±1.0 pmol/L of the control group ($F[2,128]=0.10$, $P<.9$). If the findings of elevation of TT_4 levels, but no elevation of FT_4 levels, in PTSD are viewed together and expressed quantitatively in terms of the FT_4/TT_4 ratio, the mean ratio values of 0.166±0.01 in the pilot group and of 0.188±0.01 in the present overall sample are significantly lower than the mean value of 0.233±0.01 in the control group ($F[2,128]=9.26$, $P<.0002$), indicating an imbalance characterized by *less* FT_4 vs *more* TT_4 in PTSD.

EXTENSION OF THE STUDY TO SERUM T_3 LEVELS

As indicated in the discussion of Figure 1, one possible explanation for the lowered FT_4/TT_4 ratio in PTSD might be an increased rate of conversion of FT_4 to T_3 in peripheral extrathyroidal tissues, where about 80% of circulating T_3 is produced, so that the measurement of T_3 levels represents an important next step in searching for a mechanistic explanation of the pilot findings.

TT_3 Levels

The bar graph portion of **Figure 4** presents a comparison of the mean initial TT_3 level of all 96 patients (2.7±0.06 nmol/L) with that of the 24 control subjects (2.0±0.08), showing a highly significant elevation in the overall PTSD sample ($t=6.14$, $P<.00001$). With regard to replication of this finding in the four successive 24-patient PTSD groups, Figure 4 also presents all the raw individual and group TT_3 data and shows the consistency with which all PTSD patient groups had significantly higher mean levels than the control group ($F[4,119]=13.28$, $P<.0001$; controls<1-MP=2-WH=3-WH=4-WH). The mean TT_3 levels were in the upper part of the clinical endocrinologic "normal range," and 21% of the patients had values that actually exceeded the upper limit of 3.1 nmol/L into the zone associated with T_3 thyrotoxicosis. It is also striking that 64% of the patients with PTSD had values that exceeded the upper limit of the range of the control subjects and 98% of the patients had values that exceeded the control mean value. It should be emphasized, then, that the TT_3 elevation in patients with PTSD is substantially greater in magnitude and frequency than the TT_4 elevation described above.

This marked TT_3 elevation in PTSD also appeared to be persistent over time in the subsample of West Haven patients (n=63) studied both at admission (2.8 nmol/L) and at discharge (2.5±0.06 nmol/L). While these values showed a significant decline in the discharge period ($t=3.38$, $P<.001$), the discharge level remained significantly higher than the control mean value of 2.0+0.06 nmol/L ($t=5.78$, $P<.00001$). Some individual patients and individual groups showed considerable change in levels over time, so that episodic or phase fluctuation can be superimposed on top of the persistently high baseline TT_3 levels in PTSD. It is clear, therefore, that the identification of the clinical and psychological correlates for both acute and long-term changes in TT_3 levels in PTSD are an important goal for future research in this field.

FT_3 Levels

The bar graph portion of **Figure 5** presents a comparison of the mean initial FT_3 level of all 96 patients (5.11±0.11 pmol/L) with that of the 24 control subjects (4.06±0.15 pmol/L), showing a highly significant elevation in the overall PTSD sample ($t=4.67$, $P<.00001$). With regard to replication of this finding in the four successive 24-patient PTSD groups, Figure 5 also presents all the raw individual and group FT_3 data and shows the great consistency with which all the PTSD patient groups had significantly higher mean FT_3 levels than the control group

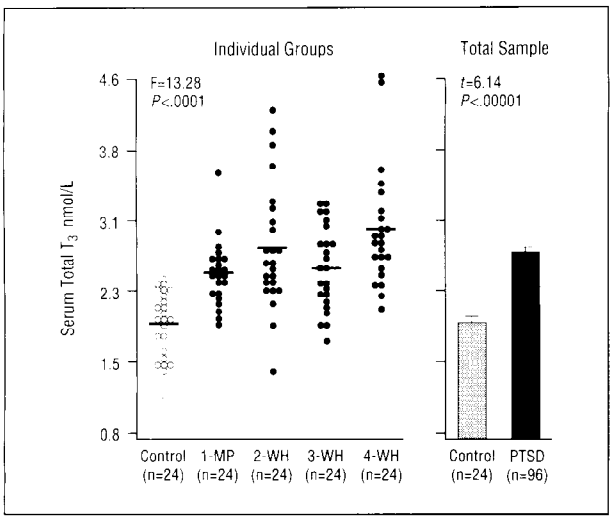

Figure 4. *Total triiodothyronine (T_3) elevations in four samples of patients with posttraumatic stress disorder (PTSD). See Figure 2 for explanation of groups.*

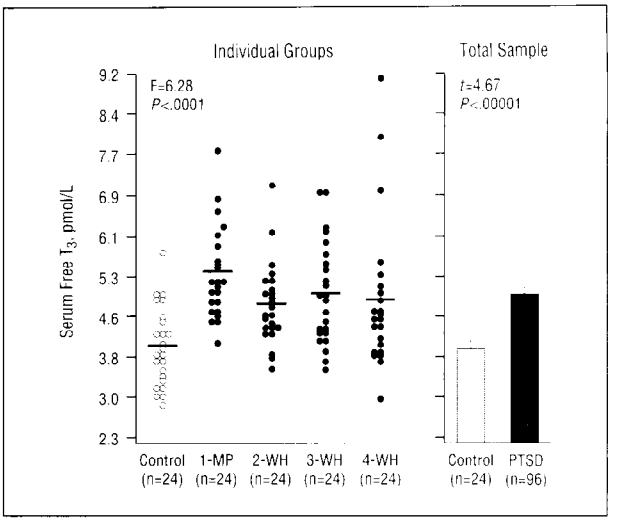

Figure 5. *Free triiodothyronine (T_3) elevations in four samples of patients with posttraumatic stress disorder (PTSD). See Figure 2 for explanation of groups.*

($F[4,119]=6.28$, $P<.0001$; controls<1-MP=2-WH=3-WH=4-WH). The mean FT_3 levels of the PTSD groups are in the upper middle part of the clinical endocrinologic "normal range," and only 8% of the patients had values that exceeded the upper limit of 6.76 pmol/L. The preponderance of patient values above the control values, however, was again evident, with 45% of the patients having levels above the values of all but one of the control subjects, and 87% of the patients had values exceeding the control mean value.

Persistence of the elevation in FT_3 levels is supported by the data from the West Haven patients (n=63) studied at two points in time, the mean value at discharge (5.15 ± 0.12 pmol/L) being significantly higher than both the admission value (4.99 ± 0.12 pmol/L) ($t=2.17$, $P<.03$) and the mean control value (4.06 ± 0.15 pmol/L) ($t=4.97$, $P<.00001$). There was moderate fluctuation in FT_3 levels at times in both individual patients and individual groups, but in general there was considerably less episodic or phase fluctuation than was observed for TT_3 levels.

EVALUATION OF THE INCREASED T_3 CONVERSION HYPOTHESIS

The finding of marked and sustained elevations of both TT_3 and FT_3 levels, in the face of only a moderate elevation of TT_4 level and no significant change in FT_4 level, appears to indicate that serious consideration should be given to the hypothesis that there may be an increased rate of peripheral extrathyroidal conversion of T_3 from deiodination of T_4 in PTSD, as postulated earlier in relation to the thyroid hormonal interactions outlined in Figure 1. The marked FT_3 increase alone appears to argue strongly for this hypothesis, since about 80% of T_3 is produced by this conversion process, and it would appear difficult to explain such a disproportionately large, selective increase in FT_3 levels without the principal source of T_3 production, the conversion process, being prominently involved.

A useful strategy for testing this hypothesis is the quantitative examination of the alterations in the relationships between the T_4 and T_3 measurements, as expressed in terms of various ratios. If the FT_4 level is relatively low because it is being "used up" peripherally more rapidly to produce T_3, then the most obvious expectations might be for increases in both the TT_3/FT_4 ratio and the FT_3/FT_4 ratio, indicating that levels of both TT_3 and FT_3 are disproportionately elevated in relation to the FT_4 level.

FT_3/FT_4 Ratio

As shown in the left side of **Figure 6**, there was a significant elevation in the FT_3/FT_4 ratio ($t=2.56$, $P<.01$) in the PTSD group, reflecting the degree to which FT_3 levels are disproportionately high in relation to FT_4 levels in PTSD. This finding, along with the significant elevation of FT_3 levels emphasized above, is of crucial importance in the evaluation of our hypotheses, since the FT_3 elevation cannot be explained by the increased binding hypothesis, but could most likely be explained as the result of increased peripheral conversion of T_3, although the possibility should be considered that it might also, in part, be related to an increased central stimulation of T_3 secretion from the thyroid through elevation of thyrotropin secretion.

TT_3/FT_4 Ratio

Since FT_4 is the immediate precursor of T_3 and since TT_3 represents most fully the overall pool of circulating T_3, of which about 80% is derived from peripheral conversion of FT_4, the TT_3/FT_4 ratio logically should

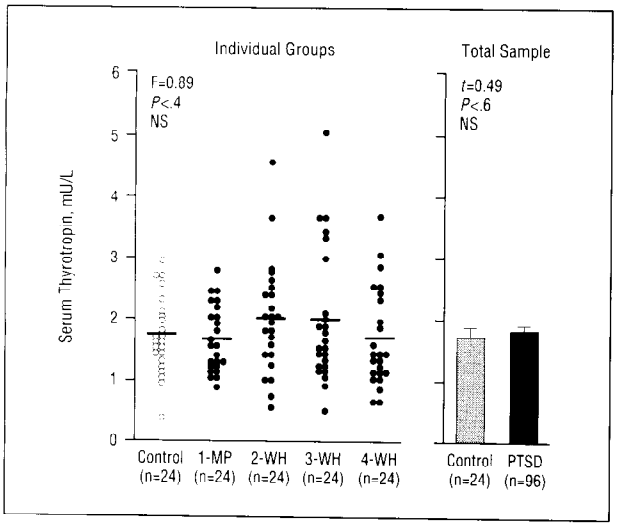

Figure 8. *Thyrotropin levels in four samples of patients with posttraumatic stress disorder (PTSD). See Figure 2 for explanation of groups. NS indicates not significant.*

high-TBG subgroup (t=5.16, P<.00001). It is also important to note that the subgroup of 51 patients with PTSD with alanine aminotransferase levels in the normal range showed a significant elevation of TBG levels, indicating some basis other than liver damage for the TBG increase. However, this suggestion that the FT_3 elevation may play a role in stimulating TBG elevation in PTSD is largely hypothetical and apparently without precedent in the literature. Nonetheless, it appears to present an intriguing possibility for further evaluation of this unexpected finding.

STUDY OF SERUM THYROTROPIN AND THE CENTRAL-STIMULATION HYPOTHESIS

Since an increase in centrally induced pituitary thyrotropin secretion leading to an increased supply of thyroid hormone might also contribute to the elevated thyroid hormone levels in PTSD, we included the measurement of serum thyrotropin levels in our assay battery. However, because thyrotropin stimulation of the thyroid gland normally contributes only a small portion (20%) to the total production of T_3, the central-stimulation hypothesis seems considerably less likely to explain the marked T_3 elevations in PTSD than does the increased T_3 conversion hypothesis.

The bar graph portion of **Figure 8** presents a comparison of the mean initial thyrotropin level of all 96 patients (1.84±0.08 mU/L) with that of the 24 control subjects (1.75±0.14 mU/L), showing no significant difference between the two groups (t=0.49, P<.6). With regard to replication of this finding in the four successive 24-patient PTSD groups, Figure 8 also presents all the raw individual and group thyrotropin data and shows the consistency with which the patient group mean levels were only slightly higher or slightly lower than that of the control group. The upper limit of the control subjects was exceeded by only 10% of the patients, and the patient group mean values varied only between 1.38±0.20 mU/L and 2.01±0.18 mU/L. Thus, thyrotropin levels generally fluctuated relatively little, remained in the middle to lower part of the clinical endocrinologic "normal range," and apparently do not have a prominent role in determining the thyroid hormone alterations in PTSD. Despite the relatively narrow range in thyrotropin levels, however, Table 1 shows a significant negative correlation between thyrotropin and FT_4 levels, which may indicate some negative feedback stimulation of thyrotropin in patients with low FT_3 levels.

STUDY OF REVERSE T_3 LEVELS

Since the levels of reverse T_3 have been useful in the characterization of some HPT axis syndromes, serum reverse T_3 levels were determined on a subsample of 20 patients with PTSD and 20 control subjects, by means of an RIA kit (Wien Laboratories Inc, Succasunna, NJ). The mean level for the patients with PTSD (0.40±0.02 nmol/L) was not significantly different (t=0.49, P<0.6) from that of the control group (0.41±0.02 nmol/L), and the values are well within the normal range of 0.28 to 0.54 nmol/L. This is an interesting finding in that TBG elevations are known to promote reverse T_3 elevations because of the strong binding affinity of the latter. In contrast, the levels of reverse T_3 are often reciprocally low when regular T_3 levels are high, so that one might speculate that in our present PTSD sample such a lowering effect may be counterbalanced by the elevating effect of the concurrent TBG elevation, with the net effect of little difference from normal.

COMMENT

The principal findings in this study are the marked and sustained elevations of FT_3 and TT_3 levels and of TBG levels in male patients with PTSD related to combat experience in Vietnam. These findings from a sample of 96 patients appear to be robust in terms of both the degree of statistical significance and the replicability in three successive 24-patient samples from the same inpatient ward, as well as in two regionally different patient samples from the East and West Coasts. In the West Haven sample studied at two points in time, the T_3 levels were significantly elevated in both the admission and discharge periods. With regard to the question of whether the T_3 changes are related to PTSD or simply to combat exposure, we found that those control subjects who were veterans with combat experience did show mean T_3 levels somewhat higher than those of subjects with no com-

bat experience, but the levels in both control subgroups were significantly lower than those in the PTSD group, so that combat exposure alone cannot explain our findings.[21]

The discovery of marked elevations in both FT_3 and TT_3 levels in PTSD appears to have some especially important practical and theoretical implications. From a purely endocrinologic standpoint, the pattern of thyroid hormone alterations in PTSD appears to be unusual, if not unique, and apparently has escaped attention up to this point largely because of the limitations of the routine clinical laboratory thyroid tests, which focus on T_4 measures to screen for the most common or classic thyroid glandular disorders. As shown in **Table 2**, the thyroid profile in PTSD is not that of classic hyperthyroidism, in which the FT_4 level is elevated and the TBG level is unchanged or decreased slightly, or that of T_3 thyrotoxicosis, in which the FT_4 level is moderately elevated and the TBG level unchanged, or that of a primary TBG increase, from liver disease or other causes, in which the FT_3 level would not be elevated. There appears to be no previously reported common or clearly recognized clinical endocrinopathy that provides an exact precedent for the unusual thyroid profile alterations in PTSD, so that we must to a large extent generate our own hypotheses about the possible mechanisms involved in the pathophysiology of this disorder.

Perhaps the pattern most closely similar to that of PTSD is that of primary TBG elevation, but while the observed elevation in TBG levels in our sample could explain part of the pattern, especially that involving high TT_4 and low FT_4 levels, the marked elevation in FT_3 levels becomes an extremely important discriminant in ruling out TBG elevation as a sole mechanistic basis for our findings. The likelihood that an additional mechanism beyond TBG elevation is operating in PTSD is supported by the finding of increases in the TT_3/FT_4 and FT_3/FT_4 ratios, which indicate that the T_3 elevations are most likely the result of increased peripheral conversion of T_4 to T_3, the process that accounts for 80% or more of the production of T_3 in the body. Of the various factors reported to be capable of increasing the rate of T_3 conversion, the elevation of peripheral catecholamine levels[13,14] appears to be the most likely underlying basis for the T_3 elevations. We have found chronic urinary catecholamine elevations to be an especially characteristic feature of the overall hormonal profile in PTSD both in our pilot study[8] and in our present large sample of patients. If it turns out ultimately that the T_3 findings are properly explained on this basis, then the uniqueness of the thyroid profile in PTSD would become understandable as a natural consequence of the chronic, marked, sustained elevations in peripheral catecholamine levels that are likewise associated with this disorder in an unusual, if not unique, fashion.[8,22] If the catecholamine-conversion hypothesis proves not to explain fully the elevated T_3 levels, then it may be necessary to consider other hypothetical mechanisms, perhaps even the possibility of direct neural stimulation of T_3 from the thyroid gland itself in relation to traumatic stress.

THE IMPRESSIVE elevation of TBG levels in PTSD also deserves some emphasis and raises some interesting questions concerning underlying mechanisms. The liver damage, commonly linked with alcohol or other drug abuse in patients with PTSD, may account for this change in some cases; however, the fact that the TBG level is elevated in many patients without active liver damage, as judged by alanine aminotransferase levels, raises the possibility that a second underlying mechanism may also be involved. In this connection, one of the most puzzling and intriguing findings in this study is the highly significant, *positive* correlation between FT_3 levels and TBG levels. If the TBG elevation were the primary driving force in this relationship, one would, of course, expect the diametrically opposite finding of a *negative* correlation between TBG and FT_3. By contrast, the actual finding appears to suggest the possibility that T_3 may be acting as the primary driving force and is stimulating a compensatory increase in TBG, perhaps in an attempt to maintain a euthyroid state in the face of chronically elevated T_3 production. In any event, this finding appears worthy of further study and may provide an important key to help in the understanding of the unusual thyroid alterations in PTSD.

The question of the clinical significance of the altered thyroid profile in PTSD, especially the T_3 elevations, is clearly important to pursue in further studies. As our work has progressed, we have been able to include an increasingly large battery of psychometric measurements of symptoms and both state and trait psychological factors that we are currently beginning to evaluate in relation to the thyroid findings.[21] As one example, in a subsample of our patients with PTSD

Table 2. Comparison of PTSD and Some Clinical Endocrinopathies*

	TT_4	FT_4	TT_3	FT_3	TBG
Hyperthyroidism	LI	LI	LI	LI	0
T_3 thyrotoxicosis	MI	MI	LI	LI	0
TBG elevation	MI	0	MI	0	LI
PTSD	MI	0	LI	MI	LI

**PTSD indicates posttraumatic stress disorder; TT_4, total thyroxine; FT_4, free thyroxine; TT_3, total triiodothyronine; FT_3, free triiodothyronine; TBG, thyroxine-binding globulin; LI, large increase; MI, moderate increase; and 0, little or no change.*

with repeated measures over time, we found some preliminary evidence of a significant relationship between T_3 levels and core PTSD symptoms, particularly "hyperarousal," as measured by the Clinician-Administered PTSD Scale rating.[21] There is a special need for further studies to determine more conclusively whether the T_3 elevations have a close relationship to such symptoms as sleep disturbances, restlessness, irritability, explosive anger, increased startle, difficulty in concentrating, anxiety, or other common features of PTSD that have also been traditionally linked with hyperthyroidism. If such relationships are found, they might strengthen the rationale for future pilot studies of various treatment approaches based on the use of such medications as propranolol and propylthiouracil, which are known to decrease the rate of the peripheral conversion of T_4 to T_3. A study by Kolb et al[23] of propranolol treatment of patients with PTSD, based on a rationale connected with the elevated sympathetic nervous system activity in this disorder, reported numerous symptom improvements, such as better sleep, fewer nightmares, less explosive anger, fewer intrusive thoughts, decreased startle response, and better psychosocial adaptation in 11 of 12 patients.

The issue of comorbidity in PTSD studies[24] is clearly important, but it is also proving to be unusually difficult to assess because of the high percentage rates and the multiplicity of the comorbid diagnoses commonly observed in Vietnam veterans with PTSD. A variety of research strategies may ultimately be required, including standard statistical analyses based on the distribution of diagnostic categories within a given patient sample, correlational analyses of hormones in relation to ratings of specific symptoms that help to discriminate between diagnostic categories, and longitudinal studies of patients with PTSD in which the time relationships between phases of hormonal change and phases of change in diagnosis-related symptoms or symptom clusters are closely examined. It will also be necessary, of course, to compare PTSD groups with groups of patients meeting diagnostic criteria for each of the major comorbid diagnoses, such as major depressive disorder, panic disorder, drug abuse, alcoholism, or borderline character disorder, but not meeting criteria for PTSD. Our work along these lines has so far not yielded any indication of important confounding diagnostic factors in relation to the T_3 elevations, but because of the large sample required for this task, we regard our current evaluation as preliminary and are continuing to enlarge our PTSD patient sample for subgroup analyses and conducting new studies with the various comparison diagnostic groups listed above.

The full implications of our findings from a clinical diagnostic standpoint remain to be determined with the future application of the present battery of thyroid measures not only to the study of comorbidity in PTSD, but also to other major psychiatric diagnostic subgroups, including psychotic disorders. In related work, we have reported that such multivariate procedures as stepwise discriminant analysis and multidimensional scaling applied to profiles of three or more hormonal measures (involving only T_4 as a thyroid measure) can yield diagnostic classification accuracy above 90% in discriminating between two psychiatric diagnostic subgroups.[25] The more complex thyroid profile used in the present study should add further discriminating power to the multidimensional approach for developing hormonal criteria to aid in the diagnosis of PTSD in future work in this field. It should also be pointed out that the hormonal profile may be especially useful in helping to discriminate between subgroups within a primary diagnostic category[8] and appears to provide a promising approach in the search for subtypes of patients with PTSD, to help evaluate the extent to which heterogeneity in patient samples is presently a confounding problem, for both clinical and research purposes.

Finally, the present study provides encouragement that the recent availability of refined new RIA micromethods from commercial sources permits a more complete assessment and "unraveling" of thyroid pathophysiology in psychiatric disorders, as foreseen by Lipton.[16] It appears that PTSD provides an example to emphasize that, although it is certainly logical to think primarily of the central aspects of HPT function in the field of stress and psychoendocrine research, it is also important to include assessment of peripheral as well as central mechanisms as fully as possible, especially in view of the unusual role of extrathyroidal mechanisms in T_3 production. While our present findings point to the special importance of a secondary peripheral mechanism in PTSD and revealed no detectable alteration in pituitary thyrotropin levels, the possible role of central HPT mechanisms in PTSD remains to be studied more fully. In an earlier pilot study, we noticed a possible tendency toward augmentation of the thyrotropin response to protirelin in some patients with PTSD,[26] but a much larger sample of patients and possibly the use of graded doses of protirelin will be required before more broad and firm conclusions can be drawn about the central level of HPT function in PTSD.

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